Influenza

2004 is the tenth anniversary of our Immunization Update broadcast. The only topic that has been included in each of these ten broadcasts is influenza. This should not be a surprise, considering the timing of this broadcast relative to influenza season, and the frequent changes in products and recommendations. The changes in this year's influenza vaccine recommendations are some of the most significant in decades, so we will again focus on this topic.

We will begin our discussion with information about the impact of influenza. More than fifty years after the introduction of an effective vaccine, influenza continues to take an enormous toll in lost lives and healthcare costs. Ten to 20 percent of the U.S. population may be infected with influenza every year, with an even higher infection rate in children

Influenza is the most frequent cause of death from a vaccine preventable disease in the United States. During 1990 through 1999, **approximately 36,000 influenza-associated pulmonary and circulatory deaths occurred during each influenza season**. Influenza seasons in which H3N2 viruses predominate are associated with higher mortality. **Persons 65 years of age and older account for more than 90% of deaths** attributed to pneumonia and influenza. Persons with underlying medical conditions account for most of the remaining 10% of deaths. **152 deaths among children less than 18 years of age were reported to CDC in 2003 and 2004.** In addition to fatalities, influenza is also responsible for an average of 114,000 hospitalizations per year. Although persons 65 years of age and older are at the highest risk of dying from influenza, other age groups are at nearly as high risk for influenza-associated hospitalization.

This table summarizes age-specific **rates of influenza related hospitalizations** per 100,000 population from several published studies. The rates among persons at high risk of complications are shown in the center column, and those not at high risk in the right column. **Children birth to 4 years** of age had rates of hospitalization higher than any other age group through age 64. The hospitalization rate among children younger than 4 years with high risk medical conditions was 500 per 100,000 population, 5 times higher than healthy children of the same age. This rate of hospitalization was higher than any other age group with high risk conditions through age 64, and in some of the studies even higher than people **65 years and older** with high risk conditions.

The risk of complications and hospitalization is not equal for all children. This table shows rates of influenza related hospitalizations by age of a Medicaid population in Tennessee. By far the highest rates of hospitalization were among **children 11 months of age and younger**, particularly those with high risk conditions, shown in the center column. But rates of hospitalization are very high

through 2 years of age in both healthy children and those with high risk conditions. Rates of hospitalization in children younger than 2 years are similar to those of persons 65 and older with high risk medical conditions.

In 2002 the Advisory Committee on Immunization Practices and the American Academies of Pediatrics and Family Physicians *encouraged* providers to administer influenza vaccine to children 6 months through 23 months of age when feasible. Vaccination of household contacts of children 23 months of age and younger was also encouraged.

We knew that this recommendation was the first step toward routine annual influenza vaccination of young children. We just did not know when the next big step would be taken. It didn't take as long as we thought. Beginning in the 2004-2005 influenza season, for the first time, ACIP and the Academies have recommended routine annual influenza vaccination **for all children 6 months through 23 months of age**. In addition, vaccination is **recommended for the household contacts and out of home caregivers** of children birth through 23 months of age. This is particularly important for household contacts of infants younger than six months of age because no influenza vaccine is approved for this age group in the United States.

Vaccination of all children 6 through 23 months of age, as well as their parents and siblings will be a formidable challenge for many practices, particularly since all this vaccination needs to be done in October and November. It is not necessary for you to reinvent the wheel as you prepare for this task. In November 2002 the National Foundation for Infectious Diseases convened a panel of experts to discuss ways to increase influenza vaccination rates among healthy and high risk children. The panel reviewed data on influenza disease burden and epidemiology, efficacy and safety of influenza vaccine, as well as barriers to pediatric influenza immunization, and ways to overcome them. The findings and conclusions of the panel were published in 2003 in this document – **Increasing Influenza Immunization Rates in Infants and Children: Putting Recommendations Into Practice**. The document includes a comprehensive review of proven strategies that providers may adapt for their practices. I would like to review these strategies briefly. Many will already be familiar to you.

The first strategy for influenza vaccination is the same one recommended for all vaccination practices – **reminder and recall systems**. These systems can be anything from a shoebox with self-addressed postcards to computerized systems with autodialers. Reminders can be targeted to parents of high risk children, parents of children younger than 2 years of age, or sent to the entire practice population. Recall systems will be particularly important to get children in for the second dose of influenza vaccine a month later. Reminder and recall systems work, and should be used by all practices that administer vaccines to persons of any age.

The second strategy, also recommended for all practices that provide vaccines of any kind, is a **practice assessment**. What providers believe is happening in their

practices rarely matches reality once charts are examined carefully. One simple way to assess progress through time is to keep track of the number of influenza vaccine doses administered each year.

The third strategy is **use of standing orders**. This allows children to be screened and vaccinated by a nurse or other staff without a specific order from a physician. Standing orders are also a proven strategy to increase vaccination levels in other practice settings.

Establishment of influenza clinics means setting aside specific hours within the practice for delivery of only influenza vaccine. This strategy can help increase rates of vaccination and also decrease costs of administration.

Mass influenza immunization programs at clinics and large practices that include pediatric, adult, and geriatric patients have resulted in delivery of thousands of doses of influenza vaccine in single day sessions. Pediatric practices should strongly consider making vaccine available to parents and siblings of children, which can increase household coverage and may also generate income for the practice.

Methods and materials for **parent education** are critical to the success of your influenza vaccination program. Parents should be educated in the office about the importance of pediatric influenza vaccination, and be given materials to take home. Parent education materials are available from NFID, CDC's influenza website, and other sources.

Finally, your **office staff must be educated** about the importance of influenza vaccine and the need to educate and inform parents at every opportunity. Everyone in your office should be vaccinated to protect themselves, and to prevent spread of influenza to your patients. You must lead by example.

Be sure to get a copy of this free, informative document from the National Foundation for Infectious Diseases website. And read it! It will help make your influenza vaccination program a little less daunting. We will have a link to the document on our broadcast resources website.

One final point about the operational aspects of pediatric influenza vaccination. Beginning in March 2003 the group of children eligible for influenza vaccine coverage through the Vaccines For Children, or VFC program was expanded to include all VFC-eligible children 6 through 23 months of age. VFC will also provide vaccine for children 2 through 18 years of age who are household contacts of children 23 months of age and younger. There is also a VFC contract for live attenuated influenza vaccine this year. We will discuss this vaccine later.

As you know, ACIP updates its influenza vaccine recommendations every year. This year's ACIP statement was published in May 2004. There were other changes in addition to the pediatric vaccination recommendation. Additional changes in this year's recommendations are the **2004-2005 vaccine virus strains**; the recommendations for vaccination of **pregnant women**; and two changes regarding **live attenuated influenza vaccine** – use of LAIV among close contacts of **immunosuppressed persons, including healthcare workers**, and guidance on who may **administer** LAIV. We will discuss each of these issues.

First, though, we would like to talk about the timing of your influenza vaccination program this year. As you are aware, there were substantial delays in the distribution of influenza vaccine in 2000 and 2001. In response, ACIP has recommended a tiered influenza vaccination program, with high risk persons to be vaccinated in October, and healthy persons vaccinated later. Current estimates are that the three manufacturers of influenza vaccine will produce between 90 and 100 million doses of influenza vaccine this year. At this point, production appears to be on schedule. However, CDC has not yet made a decision about suspension of the tiered influenza vaccination schedule for this year. We are told that this issue will be decided in the next week or so, and that a notice to readers is planned for the August 27 edition of MMWR. So watch for that publication next week. Here are two more points about the timing of influenza vaccine. To avoid missed opportunities for vaccination of **persons at high risk for serious complications, such persons should be offered vaccine beginning in September during routine healthcare visits or during hospitalizations**, if vaccine is available. **In facilities housing older persons, such as long term care facilities, vaccination before October should be avoided.** This is because antibody levels in such persons can begin to decline within a few months after vaccination. **ACIP does NOT recommend a second dose of influenza vaccine in the same season except for children younger than 9 years of age being vaccinated for the first time**. This is a very common question we receive. For adults, only one dose per season is recommended, even if the first dose was given in September.

There seems to be a perception that influenza vaccination is an October activity. It has been difficult to convince providers to continue providing vaccine to their patients into December and beyond. It is critical that we change this perception. This **graph** shows the month in which **influenza activity peaked in the United States from 1976 through 2004**. Influenza activity peaked in December in only 14% of seasons. Activity peaked in January in 21% of seasons and in February in 43% of seasons. The message here is that December is *not* too late to receive influenza vaccine. Vaccination in January or even February can still prevent a lot of influenza. ACIP recommends that providers **continue to offer influenza vaccine in December, especially to those at high risk of complications and to healthcare workers**. Providers should **continue to vaccinate throughout influenza season** as long as vaccine is available, even after influenza activity has been documented in the community.

Let's review briefly groups at increased risk for complications of influenza. Age is an important risk factor, particularly for those 65 years and older, and children younger than 24 months of age. In addition to age, the medical conditions that increase the risk of influenza complications include: **pulmonary** disease such as emphysema and asthma; **cardiovascular** disease; and **metabolic** disease such as diabetes. Additionally, **renal dysfunction**, like chronic renal failure or nephropathy; **hemoglobinopathy**, like sickle cell disease; and **immunosuppression, including HIV** are high risk conditions. In addition to persons with chronic illnesses, other risk groups include **residents of long term care facilities** and persons 6 months to 18 years of age receiving **aspirin therapy** because of the risk of Reye syndrome. Finally, **pregnant women** should be routinely vaccinated. The recommendation for vaccination of pregnant women has changed for the 2004- 2005 influenza season.

Pregnant women are a group at increased risk for complications of influenza. Excess deaths from influenza among pregnant women were documented during the pandemics of 1918-1919, and 1957-1958. Case reports and limited studies also indicate that pregnancy can increase the risk for serious medical complications of influenza. A study published in 1998 found that the **risk of hospitalization** for influenza-related complications was **more than 4 times higher for women in the second or third trimester of pregnancy than for nonpregnant women**. The risk of complications for these pregnant women was **comparable to nonpregnant women with high-risk medical conditions.** Beginning in the 2004- 2005 influenza season, **ACIP recommends vaccination with inactivated influenza vaccine for *all* women who will be pregnant during influenza season**. This is a change from the previous recommendation for vaccination of women who would be in the second or third trimester of pregnancy during influenza season. Pregnant women should receive only inactivated influenza vaccine. Live attenuated influenza vaccine is contraindicated during pregnancy. Pregnant women may receive inactivated influenza vaccine either with or without thimerosal as a preservative.

So far we have discussed vaccination of persons who are at increased risk of complications of influenza. It is also critical to vaccinate persons who are in close contact with persons at increased risk of complication. This group includes **healthcare providers**, including home care, **employees of long-term care facilities**, and **household members of high-risk persons**

Healthcare workers are a high priority for early supplies of influenza vaccine. Healthcare workers are often implicated in introducing influenza into healthcare settings and causing outbreaks among patients. Outbreaks among patients have been reported in a number of healthcare settings including ICU, neonatal intensive care units, and nursing homes. Healthcare workers often work while ill, exposing vulnerable patients and their coworkers to influenza. In addition, healthcare workers may be able to spread influenza even if they are not symptomatic since influenza viruses can be shed 1 day before symptoms develop. To make matters even worse, about half of influenza infections are

asymptomatic. So even someone who does not develop symptoms or has very mild symptoms may be able to transmit influenza to another person.

Vaccination of healthcare workers has been associated with **reductions in death among nursing home residents** based on 2 randomized studies. Vaccination of healthcare workers is also associated with **reductions in overall illness in nursing home residents**. Vaccination can also reduce the risk of influenza infection. A reduction in **illness and illness-related absenteeism** among adults has been demonstrated in several studies. Despite known benefits of influenza vaccination to both their patients and themselves, **only 38% of US healthcare workers were vaccinated in 2002**. That means nearly two out of three healthcare workers put themselves, their families, AND their patients at risk of a potentially deadly infection.

Healthcare workers cite a number of reasons – excuses, really - for not receiving influenza vaccine. These include **concern about vaccine adverse events** or vaccine safety, including the misperception that the injectable vaccine could cause influenza; a **perception of a low personal risk of influenza virus infection**; **inconvenience** of receiving the vaccine; **ignorance of CDC recommendations** for vaccination; and **dislike of needles**.

Healthcare workers owe it to their patients, their families, and to themselves to be vaccinated. No excuses. Steps to encourage healthcare worker vaccination include **reduction of financial and time barriers**; **education** about the need to protect themselves and patients; **role modeling and support by institutional leaders**; **incorporating influenza vaccination programs into the institution's patient safety and occupational health programs**; and **monitoring and reporting of vaccination rates** in the institution. Monitoring and reporting vaccination rates could be used to create friendly competition between various units in the facility. You could even provide an incentive to the unit with the highest vaccination rate. If workers won't be vaccinated to protect themselves and their patients, they might do it for a pizza.

You have new resources this year to help improve the influenza vaccination levels of your employee population. The first is a guide to improving influenza vaccination rates in healthcare workers published by the National Foundation for Infectious Diseases. The document is available on their website at **www.nfid.org**. The second resource is from the Association for Professionals in Infection Control and Epidemiology. APIC calls its toolkit "Protect your Patients. Protect Yourself". It contains a variety of materials such as a PowerPoint presentation, case studies, prototype employee newsletter articles and month by month checklists. The toolkit is available on the APIC website at **www.APIC.org**.

In addition to material from NFID and APIC, the Immunization Action Coalition also has useful materials on their website including fact sheets, prototype standing orders documents, and vaccine information statements in many languages. We will have a link to all these materials on our broadcast resources webpage.

The majority of the influenza vaccine available in the U.S. is inactivated subunit vaccine. The two types of subunit vaccine available contain either split virus, or purified hemagglutinin. A live attenuated influenza vaccine administered by nasal spray is also available again this year. We will discuss this vaccine in more detail in a few minutes.

All available influenza vaccines – including the live attenuated vaccine- are trivalent- meaning they contain 3 different viruses, two type A viruses and one type B. The viruses contained in the vaccine are chosen each spring, based on surveillance of current circulating strains. The vaccine recommended for the 2004 - 2005 season includes **A/Fujian/411/2002**- the H3N2 strain; **A/New Caledonia/20/99**- the H1N1 strain, and **B/Shanghai/361/2002**. You will recall that the A/Fujian strain is the strain that appeared early last year but was not in last year's vaccine. For the A/Fujian virus, manufacturers will use the antigenically equivalent A/Wyoming/3/2003 strain. It is also likely that a different but antigenically equivalent B strain may be substituted for the B/Shanghai.

All influenza vaccine is made from highly purified, egg grown viruses. Because the vaccine viruses are initially grown in embryonated hens eggs, the vaccine might contain a small amount of residual egg protein. Live attenuated influenza vaccine contains a substantial amount of egg protein. Consequently, influenza vaccine generally should not be administered to persons with anaphylactic egg allergy.

The inactivated influenza vaccination schedule is relatively simple – one *intramuscular* dose per year. But the dose is not the same for all age groups, and some recipients need 2 doses. Here is the routine schedule for influenza vaccine. The minimum age is 6 months. No influenza vaccine is approved for children younger than 6 months. Children **6 months through 35 months** of age receive a dose of 0.25 ml – half the dose of an older child and adult. Recipients **3 years of age** and older should receive a ½ ml dose. Children **6 months through 8 years** of age receiving influenza vaccine for the *first* time should receive *two* doses, separated by one month. The first dose is an immunologic primer. Two doses are not necessary for persons **9 years or older**, because by this age our immune systems have been primed the hard way- with wild influenza virus.

What if a child is receiving influenza vaccine for the first time, and does not return for the second dose a month later. Does the child need one or two doses the following year? This will be a common occurrence this year because of the supply problems we encountered last year. Fortunately, you can count last year's dose as the primer dose. The child needs only one dose this year, and in subsequent years.

For the 2004 - 2005 influenza season, the manufacturers estimate that **6 to 8 million doses of reduced thimerosal content influenza vaccine will be available.** The reduced thimerosal formulations **contain less than 1 microgram**

of thimerosal per dose, compared to 25 micrograms per dose for regular influenza vaccine. Reduced thimerosal formulations are **available from both manufacturers**. The **Chiron vaccine –** Fluvirin is **approved by FDA for persons 4 years of age** and older. It should *not* be administered to children 6 months to 4 years of age. The **Aventis Pasteur** vaccine – Fluzone- is available in two forms- a **0.25 milliliter single dose package for children 6 to 35 months of age**, and a **0.5 milliliter single dose package for children 3 years of age** and older.

ACIP believes that because of the known risks for severe illness from influenza infection, the benefit of influenza vaccine with reduced or standard thimerosal content outweighs the theoretical risk, if any, from thimerosal. The removal of thimerosal from other vaccines further reduces the theoretical risk from thimerosal in influenza vaccines.

Influenza vaccine has been available in the United States since the mid-1940s. Until recently, all influenza vaccines contained either whole inactivated virus, or virus subunits. In June 2003, the Food and Drug Administration approved this country's first live attenuated influenza vaccine, which we will refer to as LAIV. The vaccine is produced by MedImmune and marketed as FluMist. A VFC contract has been established for LAIV. The price this year is more competitive, and ACIP has relaxed some of its recommendations for LAIV. So it is likely that more of you will be using it – or receiving it – this year. So we want to review the characteristics and recommendations for the use of this product.

LAIV has several unique properties in addition to being a live virus vaccine. The live influenza viruses in the vaccine are **attenuated**, and produce **mild or no signs or symptoms** related to influenza virus infection. They are **temperature sensitive**, which means they **do not replicate efficiently** at core body temperature. This property prevents the live viruses from replicating efficiently in the lower airways. The viruses are also **cold adapted**, which means they **replicate efficiently at the cooler temperature of the upper airway**. This temperature is permissive for replication of LAIV viruses but restrictive for replication of many wild type viruses. What this means is that LAIV is able to replicate in the mucosa of the nasopharynx, which produces protective immunity against the viruses in the vaccine. On the other hand, the viruses are attenuated and do not replicate effectively in the lung, so they cannot produce influenza disease. LAIV is trivalent, and contains the same virus strains included in inactivated influenza vaccine. LAIV does not contain thimerosal or gelatin but does contain egg protein.

LAIV has been demonstrated to reduce culture confirmed influenza, febrile otitis media, and antibiotic use in children. LAIV also reduces febrile upper respiratory tract episodes, lost work days, and antibiotic use among adult recipients. However, there is no evidence at this time that LAIV reduces febrile illness or culture confirmed influenza more effectively than inactivated influenza vaccine.

LAIV contains live influenza viruses. As a result, there is a potential for transmission of these viruses from vaccinees to other persons. Vaccinated children can **shed vaccine viruses in nasopharyngeal secretions for up to 3 weeks**. In one study in a daycare setting, 80% of vaccinated children 8 to 36 months of age shed at least one virus strain for an **average of 7.6 days**. But remember that shedding does NOT equate to transmission of virus. In this study, *one* instance of **transmission of vaccine virus to a contact was documented**. The **transmitted virus retained its attenuated and cold-adapted, temperature-sensitive characteristics**. The frequency of shedding of vaccine strains by persons 5 to 49 years of age has not been determined.

Live attenuated influenza vaccine is approved by the Food and Drug Administration *only* for use among healthy persons 5 through 49 years of age. This group, including most persons in close contact with high risk groups, and those wishing to reduce their risk of influenza, now have the option for choosing either inactivated vaccine or LAIV.

This table shows the vaccination schedule for LAIV based on age and prior influenza vaccination history. A dose of LAIV is 0.5 milliliter, regardless of age, divided equally between nostrils. **Children 5 to 8 years of age who have received *no* previous influenza vaccine**- either LAIV or inactivated influenza vaccine- should receive **two doses of LAIV separated by 6 to 10 weeks**. Note that this is longer than the 4 weeks recommended between the first two doses of inactivated influenza vaccine. ACIP recommends that **children 5 to 8 years of age previously vaccinated** at any time with either LAIV or inactivated influenza vaccine receive **one dose** of LAIV. They do not require a second dose. This is different than the manufacturer's labeling, which recommends that children who have not previously received LAIV should receive two doses, regardless of whether they may have previously received inactivated influenza vaccine. Persons **9 through 49 years** of age should receive one dose of LAIV. LAIV is approved for use *only* in healthy persons 5 through 49 years of age.

LAIV is *not* approved for, and is not recommended for administration to most persons for whom inactivated influenza vaccine has been recommended for many years. Persons who should *not* receive LAIV include **children younger than 5 years of age**; **persons 50 years of age and older; persons with asthma, reactive airways disease or other chronic pulmonary or cardiovascular conditions**. These persons should receive inactivated influenza vaccine. Persons with other underlying medical conditions should not receive LAIV. These conditions include **metabolic disease such as diabetes**, **renal disease**, or **hemoglobinopathy, such as sickle cell disease**; and **children or adolescents receiving aspirin or other salicylates**, because of the association of Reye syndrome with wild-type influenza infection. Persons in these groups should receive inactivated influenza vaccine. As with all live virus vaccines, persons who are **immunosuppressed from disease**, **including HIV**, or who are receiving immunosuppressive **therapy**, should not receive LAIV. **Pregnant women** should not receive live virus vaccines, including LAIV. Immuno-suppressed persons and pregnant women should receive inactivated influenza

vaccine. Since LAIV contains residual egg protein, it should not be administered to persons with a history of **severe allergic reaction to egg or any other vaccine component**. Finally, the vaccine should not be administered to a person with a **history of Guillain Barré syndrome**.

LAIV may be administered to persons with minor acute illnesses, such as mild upper respiratory tract infection with or without fever. However, if nasal congestion is present which might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered the condition improves.

Close contacts of persons at high risk for complications from influenza should receive influenza vaccine. This reduces the risk of transmission of wild-type influenza viruses to high risk individuals. There are no data assessing the risk of transmission of LAIV from vaccine recipients to immunosuppressed contacts. But there have also been no reports of transmission to immunosuppressed contacts. In 2003, ACIP recommended that use of inactivated influenza vaccine be used for vaccinating household members, healthcare workers, and others who have close contact with immunosuppressed individuals. ACIP modified this recommendation in 2004. ACIP now states that **inactivated influenza vaccine is preferred only for close contacts of SEVERELY immunosuppressed persons who require care in a protective environment**. Practically, this means that healthcare workers and others who have contact with hematopoietic stem cell transplant patients while in isolation should not receive LAIV. This preference is because of the theoretical risk that a live attenuated vaccine virus could be transmitted to the severely immunosuppressed individual and cause disease. ACIP states **no preference between inactivated vaccine and LAIV for vaccination of healthcare workers and others in close contact with patients with lesser degrees of immunosuppression, and all other high-risk groups**. Of course, to be eligible for LAIV the person must be 5 to 49 years of age and healthy. **Persons who receive LAIV, including healthcare workers, should refrain from contact with severely immunosuppressed persons for 7 days after vaccination.** This precaution is to avoid exposing the immunosuppressed person to the vaccine virus. Last year we heard about several instances of LAIV recipients being banned from entering hospitals. This is not necessary. ACIP recommends that **persons who receive LAIV need not be excluded from visitation of patients who are not severely immunosuppressed** or have other medical conditions.

The manufacturer's package insert recommends that LAIV not be administered concurrently with other vaccines. This is because it is not known whether concurrent administration of LAIV with other vaccines affects the safety or efficacy of either LAIV or the simultaneously administered vaccine. In the absence of specific data indicating interference, ACIP recommends that providers follow the simultaneous administration guidelines published in the "General Recommendations on Immunization." Inactivated vaccines do not interfere with the immune response to live vaccines. **Inactivated vaccines –**

such as tetanus and diphtheria toxoids – can be administered either simultaneously or at any time before or after LAIV. **Other live vaccines can be administered at the same visit as LAIV**. However, **live vaccines not administered on the same day should be administered at least 4 weeks apart** when possible.

LAIV is stored and administered unlike any other vaccine you have ever used, and it is critical that it be handled properly. We would like to spend a few minutes on this aspect of LAIV to familiarize you with it.

LAIV is an extremely fragile vaccine that has very stringent storage and handling requirements. The viruses in LAIV have no tolerance for heat. **LAIV must be stored at or below 5°F, which is minus 15°C, at all times**. The vaccine cannot tolerate storage temperature warmer than **5°F**. So **LAIV cannot be stored in a frost-free freezer**. This is because the temperature in a frost-free freezer may rise above **5°F** during the defrost cycle. LAIV **must be stored *only* in a manual defrost freezer** that can reliably maintain minus **5°F**. If you do not have access to a manual defrost freezer, then you must store LAIV in a **special manufacturer-supplied freezer box.**

Some of you might recall that last year MedImmune suspended the use of the freezer box for LAIV shipped between December 31, 2003 and March 31, 2004. This applied ONLY to vaccine shipped through March 31, 2004. Any vaccine you receive THIS year must be stored in either a manual defrost freezer or in a freezer box.

Here is a **freezer box**. It is about 15 inches wide by 9½ inches deep, by 8½ inches high, and weighs about 19 pounds. The walls of the freezer box contain a special gel that will protect the vaccine from temperature fluctuations in a frost-free freezer. The freezer box must be **placed in the freezer** for at least 4 days before it is ready to store LAIV. This is the front cover of the freezer box. Instructions for using the freezer box are included in the packaging, and are also printed on the front of the door of the box. As you can see here, the **first instruction** is to turn down the temperature of the freezer to its lowest setting. You must be *extremely* careful when you do this. The temperature of the freezer compartment can affect the temperature of the refrigerator compartment. By lowering the temperature of the freezer, you risk lowering the refrigerator temperature below 32°F, and freezing all the vaccine in the refrigerator. With the exception of MMR, refrigerated vaccines that are frozen must be destroyed. If you lower the temperature of your freezer, you *must* do it early in the morning of a work day. The temperature in both the freezer *and* refrigerator must be monitored frequently. You must *not* lower the temperature and then go home for the night, or for the weekend because of the risk of destroying the vaccines in your refrigerator. This would be a very costly mistake.

In general, you will keep the vaccine frozen until immediately before it is used, at which time you will thaw it in your hand. LAIV may also be thawed in a refrigerator. It can be stored at refrigerator temperature – which is which is 35° to 46°F or 2° to 8°C for no more than 60 hours prior to use. Any LAIV that is kept at refrigerator temperature more than 60 hours must be discarded.

The sprayer is not just a modified syringe. It is a specially designed device with a special one-way aerosol dispersion tip that produces a fine mist. The plastic clip on the plunger divides the dose in half. One half of each dose is sprayed, or misted, into each nostril. Because LAIV is administered using a sprayer device, low level contamination of the environment with vaccine virus is probably unavoidable. This caused concern about unintentional exposure to persons administering the vaccine. The risk of acquiring vaccine virus from the environment is unknown but is likely to be limited. ACIP recommends that **severely immunosuppressed persons should not administer LAIV**. Practically, that means that if a person is immunocompetent enough to go to work, he or she is immunocompetent enough to administer LAIV. However, **other persons at increased risk for influenza complications may administer LAIV**. For instance pregnant women, persons with asthma, and persons 50 years of age and older may administer the vaccine. **Gloves and masks are not required** to administer LAIV.

To sum up, live attenuated influenza vaccine will compliment, but *not replace* inactivated influenza vaccine. The most important thing to remember is that it is approved ONLY for healthy persons 5 through 49 years of age. LAIV must not be administered to children younger than 5 years, adults 50 and older, or to anyone with a medical condition that places them at high risk for complications of influenza. These groups should receive inactivated influenza vaccine. The vaccine is extremely fragile, and requires special storage conditions that you must plan very carefully. Information about the use of LAIV is included in the 2004 influenza vaccine ACIP statement. There is also a Vaccine Information Statement specific to LAIV. Both the ACIP statement and VIS are available on our broadcast resources website, and the VISs are available in Spanish from the Immunization Action Coalition website.

Pneumococcal

We have two items of interest that concern pneumococcal vaccines. The first is recommendations concerning catch up vaccination of children whose pneumococcal conjugate vaccine doses were deferred during the PCV shortage. The second is information about the impact of pneumococcal conjugate vaccine on the incidence of invasive pneumococcal disease in the United States.

As you are aware, the demand for pneumococcal conjugate vaccine, or PCV, has exceeded the supply intermittently since the vaccine was licensed in 2000. Most recently, in February 2004, production failed to meet demand, resulting in shortages. To conserve the limited supply, CDC recommended that the fourth dose of PCV be withheld from healthy children. A few weeks later it appeared that production would be limited for several months. So CDC recommended that the third dose also be withheld.

Production problems now appear to be resolved. The supply is such that in July 2004, CDC recommended to return to a routine *three* dose schedule. Some providers might continue to have difficulties obtaining vaccine because of distribution delays. However, every effort will be made to provide sufficient vaccine to all providers.

During the shortage it was necessary to ration your available vaccine. The healthy children in your practice probably received only one or two doses. We hope that you maintained a listing of children for whom PCV was deferred. These children should now be recalled, if you have not done so already, and vaccinated as age-appropriate. Your **highest priority for catch up vaccination should be to ensure that children younger than 5 years of age at high risk for invasive pneumococcal disease are fully vaccinated.** These high risk conditions include **functional or anatomic asplenia**, **sickle cell disease** and other sickle hemoglobinopathies, **HIV infection**, **immunocompromising conditions**, a **cochlear implant**, and **chronic illnesses**, such as heart or lung disease, chronic renal failure and nephrotic syndrome. Asthma alone is not considered a high risk condition unless the child is receiving high dose steroid therapy or has obstructive lung disease.

On July 9, 2004, CDC published a summary of the pneumococcal conjugate vaccine shortage in Morbidity and Mortality Weekly Report. In this report, two new groups were added to the list of children at high risk of invasive pneumococcal disease. These groups of children are **Alaska Native and American Indian children who live in Alaska, Arizona, or New Mexico**, and **Navajo children who live in Colorado and Utah**. These children have a risk of invasive pneumococcal disease more than twice the national average. As a result they should receive the standard 4-dose PCV series despite the shortage.

The second priority group for catch up vaccination is **healthy children younger than 24 months of age who have received no doses of PCV**, and **infants younger than 12 months who have received less than 3 doses**.

As children get older, the number of doses needed to complete the series goes down. So as you recall children, many of them will likely need only 1 or 2 doses. In the July 9, 2004 MMWR article, CDC announced that the vaccination shortage had improved, and that providers could return to the three dose vaccination schedule. The MMWR article included a table to assist clinicians in determining the number of doses needed to catch up children who had missed doses during the shortage. The table is an expansion of the lapsed schedule table that was published in the 2000 PCV ACIP statement. The number of doses a child needs depends on their current age, and the number and timing of prior doses. We will provide a link to the July 9 MMWR article, and the catch up table, on our broadcast resources web page.

We know that the PCV shortages of the last 2 years have been very frustrating for providers. No one wants to defer doses of any vaccine. But despite the repeated shortages, there is some good news. Data collected by the Active Bacterial Core Surveillance system suggests that the conjugate vaccine is already having an impact on invasive pneumococcal disease in young children. We asked Doctor Cynthia Whitney, a medical epidemiologist in the CDC National Center for Infectious Diseases, to tell us about this exciting trend.

Since 1995, the Emerging Infections Network Program and CDC have conducted active surveillance for invasive disease caused by Streptococcus pneumoniae and other bacteria. The surveillance system is called Active Bacterial Core Surveillance- known as ABCs. ABCs has sites in 10 states, and includes a population of more than 20 million persons. It is an active, population based, laboratory based system. In each site, surveillance personnel contact laboratories to identify cases and collect isolates. Data are aggregated and analyzed at CDC.

The first pneumococcal conjugate vaccine was licensed in the United States in February 2000. The Advisory Committee on Immunization Practices and the American Academies of Pediatrics and Family Physicians recommended the vaccine for all children younger than 2 years of age in October 2000. Despite widespread vaccine shortages that began in 2001 and persisted into early 2003, ABCs data suggest that the conjugate vaccine is already having an impact on invasive pneumococcal disease. This graphic shows the incidence of invasive pneumococcal disease among children less than 5 years of age in 1 year increments, from 1998 through 2002. 1998 and 1999 are considered the baseline years, before licensure of conjugate vaccine. In 1998 and 1999 the highest incidence rates were among children one year of age - about 210 cases per 100,000 population, and among children younger than 1 year of age - about 170 per 100,000 population. Rates among 2, 3, and 4 year old children were lower than among younger children, but still above the overall national rate of about 23 cases per 100,000 population.

Notice the decline that occurred starting in 2000, the year the conjugate vaccine was licensed. By 2002, the rate of invasive pneumococcal disease among children younger than 2 years of age- shown here by the red and yellow lines- was about 34 cases per 100,000 population. This represents a decline in incidence of approximately 75% compared to the baseline rate. Disease among 2 years olds dropped by 72% by 2002. The rates of disease in 3 and 4 year-old children have also fallen, but less than rates among younger children. However, recall that pneumococcal conjugate vaccine is not routinely recommended for children older than 2 years of age.

Vaccinating children may also be beneficial for adults. Studies suggest that transmission from children may be responsible for a fair amount of pneumococcal disease in adults. For example, adults living with young children have higher rates of nasopharyngeal carriage and higher risk of pneumococcal disease than those without a young child in the household. Available evidence also suggests that pneumococcal conjugate vaccine reduces nasopharyngeal carriage of pneumococcal strains contained in the vaccine, and so should indirectly reduce carriage and disease rates in close contacts of vaccinated children. ABCs data suggests that this is occurring. Here we see the incidence of invasive pneumococcal disease among adult age groups from 1998 through 2002. The incidence of disease has declined in all age groups compared to the baseline in 1998 and 1999. Among adults, the highest rates of disease are in those 65 years and older. This group also accounts for most deaths from pneumococcal disease in the US. In this age group, rates have fallen from about 60 cases per 100,000 population to about 43 cases per 100,000 population - a 29% reduction. An even larger decline has been seen among 20 to 39 year olds- shown here by the green line- whose rate has fallen 46% compared to baseline. This most likely represents reduced transmission of pneumococcus from children to their parents.

We believe that the decline in rates of disease I've described is a result of the use of pneumococcal conjugate vaccine. Historically, rates of invasive pneumococcal disease have varied somewhat from year to year. However, changes of the magnitude we've seen in the last few years are not what we would expect to see with this type of variation. Similarly, while use of pneumococcal polysaccharide vaccine has increased in the last few years, the increase in use isn't enough to account for what we are seeing. While these changes are very exciting, it's only the start to the story. We don't yet know how far disease will drop or if other pneumococcal strains will start to fill in the gaps created by the pneumococcal conjugate vaccine. We will continue to monitor the ABCs data closely to see what happens.

The information that Dr. Whitney presented included ABCs data through 2002. Since we recorded her presentation, provisional data from 2003 have become available. These data show a continuation of the same trend, with rates of invasive pneumococcal disease among 1 year old children and infants younger than one year of age reduced by 83% and 77%, respectively, compared to 1998. We have also seen a 30% to 40% reduction of rates among 20 to 39 year olds, and persons 65 and older. This reduction most likely reflects a herd effect. Vaccinated children are less likely to be colonized with pneumococcus, so their parents and grandparents are less likely to be exposed to the bacteria. This is great news. Not only are we protecting young children from invasive pneumococcal disease, we are also protecting their contacts. CDC will continue to monitor these data, and will bring you updates on future National Immunization Program broadcasts.

Storage and Handling

The success of your efforts to prevent vaccine preventable diseases is dependent in part on proper storage and handling of vaccines. Exposure of vaccines to temperatures outside the recommended ranges can cost your practice thousands of dollars in wasted vaccine and revaccination. Errors in storing and handling your vaccines can also result in the loss of patient confidence in your practice when repeat doses are required. Vaccines are fragile and must be kept at the recommended temperatures at all times. It is better to *not vaccinate* than to administer a dose of vaccine that has been mishandled.

Live vaccines, like varicella and LAIV, can tolerate freezing and *must* be stored in the freezer. MMR vaccine is usually stored in the refrigerator, but it can also tolerate freezing temperatures. Live virus **vaccines deteriorate rapidly after removal from the freezer,** or from the refrigerator in the case of MMR. On the other hand, **inactivated vaccines are damaged by exposure to freezing temperatures.** Inactivate vaccines exposed to freezing temperatures should not be used. However, they can **tolerate short periods of time out of refrigeration**, although potency can be adversely affected if left out too long.

Vaccines must be stored properly from the time they are manufactured until they are administered to your patients. This is referred to as the cold chain. All healthcare providers who administer vaccines should evaluate their cold chain procedures to ensure that vaccine storage and handling guidelines are being followed. Each office should **develop and maintain a detailed written storage and handling protocol**; **assign storage and handling responsibilities to one person**; **designate a backup person**, and **ensure that both of them are provided with training on vaccine storage and handling**.

Vaccine storage units must be selected carefully and used properly. Refrigerators without freezers, and stand-alone freezers, are usually better at maintaining the required temperatures. However, a combination refrigerator-freezer unit sold for home use is acceptable for vaccine storage if the refrigerator and freezer compartments each have a separate door.

Any refrigerator or freezer used for vaccine storage must be able to **maintain the required temperature range throughout the year**. It must be **large enough to hold the year's largest vaccine inventory**, and must be **dedicated to the storage of biologics**. Food and beverages should *not* be stored in vaccine storage units. **Small dorm style refrigerators** with a single exterior door may only be used to store small quantities of inactivated vaccines or MMR. They should never be used to store varicella vaccine or LAIV, because the freezer compartment cannot maintain the required temperature without freezing everything else in the unit.

Most vaccines require storage temperatures of **35° to 46°F**, which is **2° to 8°C**, with a desired **average temperature of 40°F,** or 5°C. Both varicella vaccine and LAIV must be stored in a continuously frozen state at **5°F**, which is **-15°C**, or

colder. If you are using both the refrigerator and freezer to store vaccines, be careful not to make the freezer so cold that the refrigerator temperature drops below the recommended temperature range.

Proper temperature monitoring is key to proper cold chain management. You should have a supply of temperature monitoring records like this. The record has a space for recording both refrigerator and freezer temperatures. It has a cross-hatched or colored area that gives you a visual cue when the temperature is out of range. **Check and record the temperatures twice a day** - once in the morning and once before you leave at the end of the workday. It is important to **keep temperature logs for at least 3 years**, unless state statutes or rules require a longer period. As the refrigerator or freezer ages, you can track recurring problems or identify how long problems have existed. Equally important to checking the temperatures is **to take immediate action when the temperature is outside the recommended range**. Remember, any mishandled vaccines should *not* be administered. It is especially important that inactivated vaccine that has been exposed to freezing temperature *not* be administered.

Both the refrigerator and freezer compartments should have their own certified calibrated thermometer. Here are some examples of thermometers that can be used, including **biosafe liquid**, **continuous graphic**, and **minimum maximum**. If you are using a continuous recording thermometer, even though it is recording the temperatures for you, it should still be checked twice each day to make sure the temperatures are in range.

To keep the refrigerator and freezer cold, the unit must be in good working condition, and it must have power at all times. There are several things you can do to prevent problems. Your refrigerator should have a **plug guard or a safety lock plug** so that it cannot be pulled out accidentally. **Post a warning sign at the plug and on the refrigerator**. **Label the circuit breakers** to alert janitors and electricians not to unplug the vaccine storage unit or turn the power off. And finally, you may want to **install a temperature alarm** to alert staff to after-hours emergencies, particularly if large vaccine inventories are maintained. You can help stabilize the temperature in the **refrigerator** by keeping containers of water inside. We suggest you remove the vegetable bins and put your water bottles in their place. Keep extra cold packs or blue ice in the **freezer**. This added bulk helps keep temperatures stable with frequent opening and closing of the doors, and in the event of a power failure.

Providers should also never store vaccines in the door of the freezer or the refrigerator, or in the vegetable bin. The temperatures in these areas are not stable. Use these areas to store liquid bulk and cold packs. You can store diluent that is packed separately from its vaccine in the refrigerator door, but be sure it is clearly marked.

We are frequently asked about prefilling, or drawing up doses of vaccine before they are actually needed. Questions about this are particularly common during influenza vaccination season. The National Immunization Program strongly

discourages filling syringes in advance, for a number of reasons. The most important reason to avoid this practice is that filling a syringe before it is needed **increases the risk for administration errors**. Once in the syringe, it is difficult to tell which vaccine is which. Prefilling syringes **increases the chance of vaccine wastage** and increases the risk of **inappropriate vaccine storage conditions**. Prefilling syringes **may result in bacterial growth in the vaccines** that do not contain a preservative, such as vaccines supplied in single dose vials. There are no stability data for vaccine stored in plastic syringes. Vaccine components may interact with the plastic syringe components with time and thereby **reduce vaccine potency**. As an alternative to prefilling syringes, you may want to consider using manufacturer-supplied prefilled syringes for large immunization events, such as community influenza clinics. Syringes other than those filled by the manufacturer are designed for immediate administration and NOT for vaccine storage. Vaccine manufacturers do not recommend predrawing influenza vaccine for a large influenza clinic. NIP also strongly discourages this practice.

If a limited amount of vaccine must be predrawn for a mass immunization clinic, then follow these guidelines: **Administer only one type of vaccine** at the clinic. If more than one vaccine is to be administered, **separate vaccine administration stations by vaccine type** to prevent errors. **Transport the vaccine to the clinic in the manufacturer-supplied packaging at the recommended temperature.** If the vaccine is stored in a transport container, **use an insulated barrier such as bubble wrap or brown packing paper between the vaccine and the cold or frozen packs**. **A single layer of towel over ice is *not* adequate protection**. Upon arrival at the clinic, each person who will be administering vaccine may **draw up a small quantity of vaccine to meet the initial needs of the clinic – no more than 1 vial or 10 doses**, whichever is more. The vaccine administrators can **replenish their vaccine supply and prefilled syringes throughout the day. Monitor patient flow** to avoid drawing up unnecessary doses. **Discard any syringes other than those filled by the manufacturer at the end of the clinic day.** Predrawn vaccine should not be used on subsequent days. Let me repeat that: we recommend you discard any syringes *you* prefilled at the end of the clinic day. Predrawn vaccine should *not* be used on subsequent days.

Vaccine inventory control is a critical part of vaccine quality management. Providers need to know how much vaccine they have on hand, when it arrived, and when it expires. As part of inventory control, providers should **conduct a monthly vaccine inventory** to be sure they have enough to meet their needs. However, **avoid stocking excessive vaccine supplies**, as this leads to vaccine wastage when vaccines become outdated. Also **include diluents in the stock control procedures** and ensure adequate diluent supplies are available. Vaccines may only be reconstituted with the specified diluent. Diluents are not interchangeable. Providers should **monitor the expiration date** of their vaccine and diluent supplies and **rotate stock to avoid waste from expiration**. **Expired vaccine and diluent should never be used**. Finally, to help protect your vaccine supply, **limit access to authorized personnel only**.

It is critical that every clinic have a written emergency vaccine retrieval and storage plan. The most important part of this plan is to identify a location with a backup generator where a provider can move their vaccine in the event of an emergency, such as an equipment failure or power outage. Consider contacting a local hospital, the Red Cross, or a long term care facility as a backup site. Information to assist in developing a written plan is available on the National Immunization Program website. In fact, there are a number of useful storage and handling resources in Appendix D of the Pink Book. We will provide several other helpful items on the broadcast resource website.

The National Immunization Program also has a new smallpox vaccine storage and handling training program. The program consists of four web-based self-study modules that participants can complete at their own pace. The program offers continuing education credit, and is free of charge. You can locate it through our broadcast resources web page.

Other tools will also be available soon from CDC. A vaccine storage and handling CD-ROM and a web based storage and handling training module for vaccine providers are both expected to be available in the Fall of 2004. We will announce their availability on the NIP website.

In order for patients to be protected by vaccines, vaccines must be stored and handled with care. With a few simple steps and good practices to maintain proper vaccine storage and handling, we can ensure that the full benefit of immunization is realized.

Varicella

In the prevaccination era, an estimated 3 to 4 million cases of varicella occurred every year- basically the entire annual birth cohort. But vaccination coverage in 2003 was about 85%, and there is evidence from active surveillance sites that the disease is no longer inevitable.

Data from active varicella surveillance sites have shown a more than 85% decrease in the number of varicella cases. Incidence has declined in all age groups, but particularly among children 1 to 4 years of age. In addition, the number of outbreaks, the number of school days missed due to varicella, and the number and rates of hospitalization have fallen dramatically.

We do not think this reduction in varicella is unique to the active surveillance sites. Several states conducting passive surveillance for varicella have also seen a major decline in cases in the last 3 years. Despite this clear impact on varicella disease, providers and parents continue to have concerns about the vaccine. One of the most common concerns we hear about varicella vaccine has to do with waning immunity and breakthrough disease. We asked Dr. Dalya Guris, team leader for herpes virus activity for the National Immunization Program, to update us on recent investigations of these issues.

Varicella vaccine was approved for use in the United States in 1995. Prelicensure clinical trials estimated vaccine effectiveness at 80% to 90%. Therefore, 10% to 20% of vaccine recipients will develop varicella disease, also called breakthrough varicella. However, most breakthrough cases are mild with less than 50 lesions. Prelicensure trials estimated protection from moderate or severe varicella disease at up to 95%.

In the years since varicella vaccine was licensed, CDC and state and local health departments have investigated varicella outbreaks in a variety of settings, such as child care centers and schools. The purpose of these investigations was to estimate postlicensure vaccine effectiveness, and to try to identify risk factors for varicella vaccine failure.

Seventeen outbreak investigations have estimated vaccine effectiveness at 71% to 100% for all varicella disease, with most estimates around 85%. A large case control study among children in private medical practices in Connecticut also estimated overall effectiveness at 87%. Effectiveness against moderate or severe varicella has consistently been found to be 90% to 100%, verifying that breakthrough varicella is much less severe than varicella in unvaccinated people. Three outbreak investigations estimated vaccine effectiveness of 44% to 59%. The reason or reasons these three estimates are lower than all the others is not clear. However, we generally investigate outbreaks that are unusual, and these three outbreaks were not representative of typical varicella outbreaks.

Whenever possible during studies of varicella vaccine effectiveness, investigators have attempted to identify risk factors for vaccine failure. One of the potential risk factors for breakthrough varicella is time since vaccination. If breakthrough varicella increased with increasing time since vaccination, this would suggest waning of vaccine induced immunity over time. Four investigations have found that persons vaccinated 3 to 5 years earlier were more likely to develop breakthrough varicella than those vaccinated more recently. However, the majority of investigations that were of sufficient size to investigate this issue did not identify time since vaccination as a risk for vaccine failure. The large case control study of Connecticut children

found that effectiveness decreased from 97% in the first year to 84% in years two through 8 after vaccination.

Age of vaccination has also been a concern. Some children may still have circulating maternal antibody after the first birthday. If this is the case, children vaccinated closer to a year of age might have a higher risk of vaccine failure because of maternal antibody interference, than those vaccinated a few months later. Seven investigations have found a relation between age of vaccination and breakthrough varicella. Most have found the risk of breakthrough varicella 2 to 4 times higher among children vaccinated at 12 to 14 months of age compared to those vaccinated at age 15 months or older. However, this is also not a consistent finding in outbreak investigations. Most investigations have not identified age at vaccination as a risk factor for breakthrough varicella.

Another risk factor that has been suggested for varicella vaccine failure is the presence of asthma. Two investigations have found an increased risk of breakthrough varicella among children with asthma. However, these studies did not include information about medication, such as steroids, that the child may have been taking. A retrospective cohort study examined the effect of both asthma and systemic steroids. This study found an increased risk for children taking steroids but not for those with asthma who were not taking steroids.

Taken as a whole, these postlicensure investigations have confirmed prelicensure estimates of varicella vaccine effectiveness against all varicella disease, and especially against moderate and severe illness. Although the results of a few studies have suggested otherwise, most investigations have not identified age at vaccination or time since vaccination as risk factors for breakthrough varicella. It is not clear whether asthma or steroid use at the time of vaccination increases the risk of breakthrough disease. Until more definitive information become available, the Advisory Committee on Immunization Practices will continue to recommend a single dose of varicella vaccine for all children at 12 to 18 months of age. However, ACIP will continue to monitor research in this area to ascertain the possible benefit of changes in the recommended immunization schedule.

IOM Report – Vaccines & Autism

As you know, vaccine safety concerns are common among both parents and vaccine providers. It seems that hardly a day goes by without some vaccine safety article on television, or in print, or on the Internet. One of the most persistent vaccine safety issues is the allegation of an association between measles vaccine, MMR, thimerosal, and autism. In 2000, the Centers for Disease Control and Prevention and the National Institutes of Health asked the Institute of Medicine to establish an independent expert committee to evaluate evidence regarding whether vaccines cause certain health problems, and to report their conclusions and recommendations.

In its first report in 2001, the Immunization Safety Review Committee reviewed the hypothesized association between measles-mumps-rubella vaccine and autism, which the committee rejected based on the evidence at the time. The second report in 2001 reviewed the hypothesized link between thimerosal-containing vaccines and a broad range of neurodevelopmental disorders including autism. The committee concluded that the evidence available at the time was inadequate to either accept or reject a causal relationship between thimerosal and neurodevelopmental disorders. This means that at that time, with the evidence available, the committee could not conclude one way or the other on the question. In May 2004, the Immunization Safety Review Committee issued its eighth and final report on the issue of vaccines and autism. We asked Dr. Kathleen Stratton, study director for the vaccine safety reports, to tell us about the new report.

Roy: Dr. Stratton, why has the Immunization Safety Review Committee revisited the issue of vaccines and autism?

Stratton: The Immunization Safety Review Committee first reviewed data on the association of MMR vaccine and autism, and thimerosal and neurodevelopmental disorders in 2001. These reviews – particularly that regarding thimerosal - were hampered by a paucity of well-conducted epidemiologic studies at the time. Since 2001 a lot of additional studies have been performed to examine these issues. In the May 2004 report, the committee updated its conclusions and recommendations regarding vaccines and autism based on this new information.

Roy: What new information about thimerosal and autism has become available since 2001?

Stratton: Several recent studies have examined the association between thimerosal-containing vaccines and autism.

Since 2001, three controlled epidemiological studies and two uncontrolled observational studies have been published that have found no evidence of an association between thimerosal-containing vaccines and autism. These studies utilized different methods and examined different populations in Sweden, Denmark, the United States, and the United Kingdom.

Several studies claimed to have found an association between thimerosal containing vaccines and autism. However, all these studies have serious methodological and analytic flaws and so were not helpful in the assessment. Based on this body of evidence, the committee concludes that the evidence favors rejection of a causal relationship between thimerosal-containing vaccines

and autism. This conclusion differs from the committee's finding in its 2001 report on thimerosal containing vaccines and neurodevelopmental disorders. The committee reported then that the evidence was inadequate to accept or reject a causal relationship between exposure to thimerosal from childhood vaccines, and the neurodevelopmental disorders of autism, ADHD, and speech and language delay. The committee's conclusion in 2001 was based on the fact that there were no published epidemiological studies examining the potential association between thimerosal-containing vaccines and neurodevelopmental disorders. the two unpublished, epidemiological studies that were available provided only weak and inconclusive evidence. Furthermore, the conclusion in the 2001 report pertained to a broader set of neurodevelopmental disorders, while this report's conclusion applies *only* to autism.

Roy: The possible relation of MMR vaccine and autism continues to concern parents. What information did the committee review for this part of its report?

Stratton: Since 2001 there have been many investigations into the association between MMR and autism. Fourteen studies have examined this issue, including 9 controlled observational studies, three ecologic studies, and two studies based on a passive reporting system in Finland. These studies have consistently showed evidence of no association between MMR vaccine and autism. Two studies reported an association. However, like the positive thimerosal studies by the same authors, these studies had serious methodologic and analytic flaws and were not useful as far as assessing causality. The original case series reported by Andrew Wakefield in 1998 was also not helpful in our review. Based on this body of evidence, the committee concludes that the evidence favors rejection of a causal relationship between MMR vaccine and autism. This conclusion is consistent with the finding in the committee's previous report on MMR and autism.

The committee also considered the biological mechanisms by which MMR or thimerosal could lead to autism. It's clear from twin and family studies that there is a strong genetic basis for autism. Several investigators have proposed hypothetical biologic mechanism. However the experiments being conducted to support these hypotheses lack relevance to our current understanding of the development of autism. In the absence of evidence that vaccination- either MMR or thimerosal- affects any physiologic or molecular mechanisms that are know to be causally-related to the development of autism, the committee concludes that the hypotheses regarding a link between autism and MMR vaccine and thimerosal-containing vaccines are only theoretical.

The committee believes that future research to find the cause of autism should be directed toward other promising lines of inquiry that are supported by current knowledge and evidence and offer more promise for providing an answer. The committee does not consider a significant investment in studies of the theoretical vaccine-autism connection to be useful at this time. The committee's conclusions of a lack of association between either thimerosal or MMR and autism should be really good news for both parents AND providers. We can continue to protect children with vaccines without the specter of autism over us.

Roy: What policy and research recommendations did the committee make?

Stratton: The committee made a number of recommendations in the areas of policy, surveillance, and epidemiologic research, clinical studies, and communication. First, the committee does *not* recommend a policy review of the licensure of MMR vaccine or of the current schedule and recommendations for giving the MMR vaccine to children. Second, the committee does not recommend a policy review of the current schedule and recommendations for the administration of routine childhood vaccines based on hypotheses regarding thimerosal and autism. Third, the committee recommends that cost-benefit assessments regarding the use of thimerosal-containing versus thimerosal-free vaccines and other biological or pharmaceutical products, whether in the United States or other countries, should not include autism as a potential risk. The committee heard from some parents of children with ASD who have chosen to rely on chelation therapy as a treatment. The committee saw no scientific evidence that chelation is an effective therapy for ASD, or is even indicated in children with ASD. Chelation therapy is currently

indicated only for high dose acute mercury poisoning. Because chelation therapy has potentially serious risks, the committee recommends that it be used only in carefully controlled research settings with appropriate oversight by Institutional Review Boards to protect the interests of the children who participate. Finally, the committee recommends developing programs to increase public participation in vaccine safety research and policy decisions. These programs should also enhance the skills and willingness of scientists and government officials to engage in constructive dialogue with the public about research findings and their implications for policy development. The committee also made several recommendations regarding surveillance of adverse events and following vaccination and epidemiologic research. These include the use of standardized case definitions of autism spectrum disorder and additional investigations into risk factors and biologic markers for autism. Details of these recommendations can be found in the full report. From its inception the Immunization Safety Review Committee has been supportive of ongoing vaccine safety research. The committee is also very supportive of additional research on autism in general. This disease can be devastating to a family. Better understanding of the biology of autism can help point the way to better treatment and, ultimately, to prevention.

Roy: Dr. Stratton, thank you for taking time to share this information with our audience today.

Stratton: My pleasure. Thank you.

The conclusions of the eighth and final report of the IOM Immunization Safety Review Committee were released on May 18, 2004. The full report is being printed now, and should be available from the National Academy of Sciences in the next few weeks. The National Immunization Program has a summary of the report, as well as background on measles vaccine, thimerosal and autism on their website. The website also has fact sheets on the report for both providers and parents. These fact sheets provide background on the Committee, and summarize the evidence supporting the Committee's conclusions. The fact sheets should be helpful for your staff and parents who are concerned about vaccines and autism. We will put a link to the summary materials and fact sheets on our broadcast resources website.

Vaccine Briefs

Pediarix: Our first Vaccine Brief concerns Pediarix, a new pediatric combination vaccine. Pediarix was licensed by the US Food and Drug Administration in December 2002. Pediarix contains DTaP, hepatitis B, and inactivated polio vaccines. The DTaP component is Infanrix, and the hepatitis B component is Engerix-B. Pediarix is approved for the first three doses of the DTaP and IPV series, which are usually given at about 2, 4, and 6 months of age. However, Pediarix is approved for use through 6 years of age, the same as the DTaP component. This means that a child who is behind schedule can still receive Pediarix as long as it is given for doses one, two, or three of the series, and the child is younger than 7 years of age.

One of the most common questions we receive about Pediarix is its use for the fourth and fifth doses of the DTaP series. Pediarix is not approved by FDA for these doses of the DTaP series. However, the childhood immunization schedule includes a statement about the use of combination vaccines which can cause some confusion. The rule says that **combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated**. This statement has been interpreted by some providers as allowing off-label use of Pediarix for the fourth and fifth doses of the series.

We have discussed this issue internally at the National Immunization Program, and presented it to the Advisory Committee on Immunization Practices at their June 2004 meeting. ACIP referred the issue to the groups working on the harmonized schedule and the revision of the General Recommendations, so we do not have input from them yet. The National Immunization Program's opinion is that Pediarix should be used only for the doses for which it has been approved by FDA. Since FDA has not approved Pediarix for the fourth and fifth doses, we recommend you **not use it for these doses**, regardless of the combination vaccine statement on the schedule. A possible **exception to this would be if a child is eligible for the fourth or fifth dose and Pediarix is the only DTaP vaccine available** to you. In this case it is probably preferable to use Pediarix off-label than to allow the child to leave the office without the DTaP dose.

We have received numerous inquiries about doses of Pediarix inadvertently administered as booster doses. For instance, if Pediarix administered as a child's fourth or fifth dose of DTaP can be counted as a valid dose. I will repeat here that FDA has not approved Pediarix for booster doses, so you should not use it in this situation. However, if Pediarix has been inadvertently administered as the fourth or fifth dose of DTAP or the fourth dose of IPV, it is not necessary to repeat the dose.

National Immunization Survey: The National Immunization Survey provides estimates of vaccination coverage among children aged 19 through 35 months for each of the 50 states and 28 selected urban areas. First conducted in 1994 as part of the Childhood Immunization Initiative, NIS is a quarterly random digit

dialing sample of telephone numbers for each of the 78 survey areas. The calendar year 2003 results reflected a sample of more than 21,000 children, and were released on July 29, 2004. This is what Dr. Julie Gerberding, Director of the Centers for Disease Control and Prevention, had to say about the results.

> Let me end with a hopeful perspective. This is the record year for immunization coverage in the United States. This is the record year for protecting our children from vaccine preventable diseases but we have challenges and we need your help and we need everyone to commit to protecting every child from these sometimes devastating illnesses. Thank you.

The 2003 NIS data were published in Morbidity and Mortality Weekly Report on July 30, 2004. There is a link to the report on our broadcast resources website. The 2003 results indicate that childhood immunization levels are at record high levels.

This table shows selected results from the 2003 data. Coverage for **DTaP 4**, the most difficult dose to get in, increased by an impressive 3% since 2002. Coverage for 3 doses of **hepatitis B** vaccine increased 2%, and is above 90% for the first time. This is the first full year that **pneumococcal conjugate vaccine** has been included in NIS. Even with intermittent shortages, two thirds of children had receive at least 3 doses. **Varicella** coverage increased 4% to 85%, the highest ever measured. Finally, the coverage levels for the various **combined series** increased 4% to 5%, reflecting increases in the individual antigens. This is really great news. And we know that these record high coverage levels are the result of hard work by all of you out there on the front lines. The National Immunization Program greatly appreciates all your efforts. I think you should all give yourselves a round of applause.

Despite the good news, the job is not done. There is substantial variation in coverage levels between states, and between states and urban areas. We still have a ways to go to reach the 2010 national objective of 90% for the combined vaccination series. And of course, 11,000 more children are born every day, all with a vaccination level of zero. So celebrate your successes today. Tomorrow, renew your efforts to ensure that no child, adolescent or adult will have to needlessly suffer from a vaccine preventable disease.

Vaccine Information Statements: Risk and benefit communication between the provider and the person receiving the vaccine is essential. The cornerstone of immunization patient education is the Vaccine Information Statement, or VIS. **Every healthcare provider, public or private, who administers a vaccine covered by the National Childhood Vaccine Injury Act is required by law to provide a copy of the most current VIS with *each dose* of vaccine administered**. Not only the first dose, but every dose. In addition, CDC encourages healthcare providers to use all available VISs, whether the National Childhood Vaccine Injury Act covers the vaccine or not. It is just good practice.

Healthcare providers should also encourage the patient or their representative to take the VIS home. This is important because the VIS contains information that may be needed later, including the recommended schedule for that vaccine, information concerning what to look for and do after the vaccination, and what to do if there is a serious reaction.

Healthcare providers are **not required by Federal law to obtain the signature** of the patient or their representative acknowledging receipt of the VIS. The VISs are not designed as informed consent documents. But while the federal government does not require informed consent for vaccinations, some states do. You should consult your agency or state immunization program to determine if there are any specific informed consent requirements. Documentation that the VIS was given is required. Healthcare providers **must note in each patient's permanent medical record or in a permanent office log or file,** the **date printed on the VIS** and the **date the VIS is given to the vaccine recipient, or their legal representative**. Every VIS is dated. The date is always located in the corner of the second page of the document, and sometimes on the first page as well. This is the date that must be recorded in the patient's chart. VISs change periodically. Paying attention to this date also helps to ensure that your office always has the most current version of each VIS. Speaking of most current versions, this table lists Vaccine Information Statements that are new or revised since our last Immunization Update broadcast in August 2003. There are **new statements for rabies and typhoid** vaccines, for those of you who vaccinate travelers or persons with occupational risk of rabies. VISs for **inactivated influenza vaccine, live attenuated influenza vaccine**, and **hepatitis A** vaccine have been revised. The **MMR** VIS was modified slightly for clarity. The edition date did not change. Information about the Vaccine Adverse Event Reporting System – **VAERS- was clarified on all statements**. As a general rule, it is not necessary to throw out your old statements unless a major change has been made. Just replace your supply with the new version when you run out of the older version.

All English language Vaccine Information Statements are available from the National Immunization Program and state immunization programs. VISs are available in more than 25 languages on the Immunization Action Coalition website. We will have a link to all the Vaccine Information Statements on our broadcast resources website.

Global Polio Eradication: For our last vaccine brief, we would like to update you on the status of global polio eradication. The Global Polio Eradication Initiative was launched by the World Health Assembly in 1988. At that time 125 countries were considered endemic for wild poliovirus. The World Health Organization, CDC, Rotary International, and UNICEF are the principal partners. National governments, private foundations, nongovernmental organizations, corporations, and volunteers are all collaborating to achieve eradication. In 2003, a total of 784 cases of polio were reported from 6 countries. These countries, shown on this map in red are located in 3 WHO regions – Africa, Eastern Mediterranean, and South East Asia. Almost 75% of all cases in 2003 occurred in just two countries,

Nigeria and India. In the first half of 2004, Nigeria accounted for 78% of cases reported globally.

Three endemic countries – Egypt, India, and Pakistan, recorded their lowest ever levels of transmission during the second half of 2003. Unfortunately, 51 imported cases were reported by 10 countries previously considered polio free. This is the first time that the number of countries reporting importations was larger than the number of endemic countries. Eight of these countries are in west and central Africa.

The largest increase in cases occurred in Nigeria. In August 2003, several northern Nigerian states suspended polio vaccination programs because of rumors that the vaccine had been adulterated with HIV and infertility agents. Fortunately, the ban on OPV was recently lifted and vaccination programs began again in July.

Several challenges to global eradication remain. These include: **maintaining high-quality surveillance and immunization activities; gaining access to children in conflict affected countries; providing sufficient oral polio vaccine; and ensuring political and financial support** until certification of global eradication can be achieved.

You may be able to help meet at least one of these challenges. CDC continues to recruit healthcare professionals for short-term field assignments to polio endemic countries. This program is called Stop Transmission of Polio, or STOP. During a 3 month assignment team members may **conduct and evaluate active surveillance**; **assist with case investigations and follow-up** as well as conduct measles outbreak investigations; help to **plan, implement and evaluate supplemental immunization activities** such as national immunization days; and **develop and strengthen data management systems for the national immunization programs**. A STOP team assignment is not for everyone. But it can be a very rewarding experience. We will provide a link to information about the STOP program on our broadcast resources website.